

## APPLICATION UNDER UNITED STATES PATENT LAWS

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Invention: FAST DISINTEGRATING TABLETS AND METHOD FOR PRODUCTION THEREOF

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## SPECIFICATION

DESCRIPTION

FAST DISINTEGRATING TABLETS AND METHOD FOR  
PRODUCTION THEREOF

TECHNICAL FIELD

The present invention relates to surface-modified powders comprising a pharmacologically active ingredient and having a good flowability sufficient to  
5 enable direct tabletting, a method for preparing the surface-modified powders and use thereof, as well as fast disintegrating tablets, which have a suitable strength and dissolve instantly in the mouth when holding water in the oral cavity, and a method of  
10 producing the tablets using the surface-modified powders comprising a pharmacologically active ingredient.

BACKGROUND ART

Recently, research has been extensively  
15 undertaken to develop orally dissolving preparations having an appropriate disintegratability and solubility to make oral medication easy to the elderly people and infants.

According especially to the silver science  
20 research conducted by the Japanese Ministry of Health and Welfare, there is an interesting research report entitled "Studies to manufacture new pharmaceutical

preparations and new packaging containers most suitable for administration to elderly people" (Masayasu Sugihara, et al., Tokyo Women's Medical College) (Yakuji Nippo, August 22, 1989 issue). The report  
5 discloses buccal dissolution type preparations containing polyethylene glycol 1000 as the base that dissolves in the oral cavity, and oleaginous base as the base that melts at the temperature in the oral cavity, which preparations are obtained by filling the  
10 pocket of a polyvinyl chloride molding sheet for press through package (PTP) use with a medicated base, and allowing to cool and mold.

Japanese Patent KOKAI (Laid-Open) No. 5-271054 discloses buccal dissolution type tablets having  
15 a porous structure with a hardness of 2 to 25 kg and a porosity of about 20 to 80%, which are manufactured by tableting a composition comprising a pharmacologically active ingredient, a carbohydrate and water in an amount barely sufficient to wet the surface of  
20 particles of the carbohydrate.

On the other hand, in certain countries, buccal dissolution type solid preparations, such as Zydis (trade name) from R. P. Scherer (England) etc., are commercially available. The Zydis preparation is  
25 manufactured by blending a pharmacologically active ingredient, a polymer, sugar and other ingredients together, dissolving the blend and freeze-drying the solution (Manuf. Chemist., February 36, 1990).

However, since the buccal dissolution type tablets described above are administered by dissolving in the mouth on contact with saliva, these tablets are not necessarily compatible with practical dosing instructions in the actual medical scene, namely, the dosage form of giving a medicament with a cup of water. It is therefore concerned that confusion might be caused in the actual medical scene. Also, 2 or 3 kinds of drugs are simultaneously administered mostly in practical medication and even 5 or 6 kinds of drugs are given all together in some occasion. Then, it tends to occur such a case that only one medicament is taken without water because of its buccal dissolution tablet form but the other medicaments should be taken with water, which also tends to cause confusion.

The aforesaid methods for preparing buccal dissolution type tablets all involve difficulties in tablet preparation via complex procedures including heating, melting, dissolution, freezing and the like. It is thus desired to prepare buccal dissolution type tablets in a simple way, e.g., by dry granulation, direct tableting, etc.

However, since powdery active ingredients are poorly flowable, dry granulation technique has been used only for well-fluidizing pharmacologically active ingredients. Physically, direct tableting of ordinary active ingredients with a small bulk density and poor fluidizing properties is considered extremely difficult

since the direct tableting is greatly affected by the powder characteristics and proportion of pharmacologically active ingredients. Very few attempts to improve powder properties of a pharmacologically active ingredient at the final stage of overall synthesis steps have been hitherto made but the purpose was to avoid problems upon tableting. Actually, high dose preparations of a pharmacologically active ingredient are very rarely manufactured by direct tableting.

10 For these reasons, any report to study dry granulation and direct tableting of buccal dissolution type tablets has not yet been made.

#### DISCLOSURE OF INVENTION

Therefore, it is an object of the present invention to provide fast disintegrating tablets, which have a suitable disintegratability and solubility to be disintegrated to an appropriate size when holding water in the oral cavity so that the tablets are neither adhered to nor choked in the throat, and are easy for aged or pediatric patients to take medicaments, which can still maintain a mechanical strength sufficient to resist destruction in the course of manufacture and storage, and which also have an adequate strength to resist crumbling upon administration, for example, when they are taken out of PTP packages.

It is another object of the present invention to provide a method of producing fast disintegrating

tablets by dry granulation technique, in which tablets having the aforesaid excellent properties can be produced in a simple fashion, without requiring complex manufacturing procedures.

5           It is a further object of the present invention to provide surface-modified powders comprising a pharmacologically active ingredient having a good flowability, which enables to produce, by direct  
10   tableting and dry granulation technique, the aforesaid fast disintegrating tablets that are readily taken by aged or pediatric patients and are thus practically useful.

          It is a further object of the present invention to provide a method for producing the surface-  
15   modified powders comprising a pharmacologically active ingredient with a good flowability.

          It is a still further object of the present invention to provide use of surface-modified powders comprising a pharmacologically active ingredient for  
20   producing tablets by direct tableting of the surface-modified powders comprising a pharmacologically active ingredient.

          It is a still further object of the present invention to provide a method of producing tablets,  
25   which comprises producing tablets by direct tableting using the surface-modified powders comprising a pharmacologically active ingredient.

~~In view of the circumstances described above,~~

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the present inventors have made extensive investigations to develop tablets of fast disintegration type and found that, when a pharmacologically active ingredient is subjected to surface modification with a surface modifying base material such as light silicic anhydride, etc., the surface-modified powders comprising a pharmacologically active ingredient with a good flowability can be obtained. The inventors have further found that blending of the surface-modified powders comprising a pharmacologically active ingredient with a disintegrant such as partially alphanized starch, crospovidone, etc. followed by direct tableting provides fast or rapidly disintegrating tablets that maintain an adequate hardness and are yet rapidly disintegrated and dissolved in the oral cavity without resort to complex production procedures such as heating, melting, dissolving, freezing, etc.; these complex procedures are usually required for conventional production steps. Based on the above findings, the present invention has been accomplished.

Therefore, the present invention relates to surface-modified powders comprising a pharmacologically active ingredient having a flowability sufficient to enable direct tableting, the powders being surface-modified by subjecting powders for surface modification comprising a pharmacologically active ingredient or a pharmacologically active ingredient and a diluent to surface modification with a surface modifying base

material.

The present invention further relates to a method of producing pharmacologically active ingredient-comprising surface-modified powders, which  
5 comprises blending powders for surface modification comprising a pharmacologically active ingredient or a pharmacologically active ingredient and a diluent with a surface modifying base material to modify the surface of the powders, whereby the pharmacologically active  
10 ingredient-comprising surface-modified powders having flowability sufficient to enable direct tabletting are produced.

The present invention further relates to a fast disintegrating tablet obtained by blending the  
15 pharmacologically active ingredient-comprising surface-modified powders described above with a disintegrant and directly tabletting the blend.

The present invention further relates to a method of producing a fast disintegrating tablet, which  
20 comprises blending modifying powders comprising a pharmacologically active ingredient or a pharmacologically active ingredient and a diluent with a surface modifying base material to modify the surface of the powders thereby to prepare pharmacologically  
25 active ingredient-comprising surface-modified powders having flowability sufficient to enable direct tabletting, then incorporating a disintegrant into the powders, and directly tabletting the mixture to produce



the fast disintegrating tablet.

The present invention further relates to use of pharmacologically active ingredient-comprising surface-modified powders for the production of tablets  
5 by directly tableting the pharmacologically active ingredient-comprising surface-modified powders optionally after adding an additive(s) to the powders.

#### BEST MODE FOR CARRYING OUT THE INVENTION

The pharmacologically active ingredient for  
10 use in the present invention may be in any optional form so long as the active ingredient takes a powdery form at ambient temperature. The active ingredient may also be in a crystalline or non-crystalline form. When pharmacologically active ingredients take no powdery  
15 form at ambient temperature, these active ingredients may be converted into a powdery form at ambient temperature by adsorbing these active ingredients onto a porous carrier such as special calcium silicate, starch, etc.

20 Specifically, the pharmacologically active ingredients for use in the present invention may be at least one member selected from the group consisting of gastrointestinal function conditioning agents, antacids, analgesics, antiinflammatory agents, anti-  
25 inflammatory-analgesic-antipyretic agents, anti-bacterial agents, antifungal agents, cardiotonics, inorganics preparations, therapeutic agents for

digestive ulcer, coronary vasodilators, peripheral vasodilators and cerebrovasodilators, anti-infectives, anti-anxiety drugs, neuroleptic agents, central nervous system stimulants, antidepressants, antihistamines, antidiarrheal preparations, mild laxatives, nourishing and health-promoting agents, cholesterol lowering agents, spasmolytics, antiagony agents, heart rhythm regulators, therapeutic agents for arterial hypertension, antimigraine agents, blood coagulation regulators, therapeutic agents for thyroid dysfunction, diuretics, appetite suppressants, antiasthmatics, antitussives, expectorants, sedative expectants, mucus controlling agents, antiemetics, anti-uricemic agents, therapeutic agents for gout, antiarrhythmic drugs, therapeutic drugs for hyperglycemia, bronchodilators, antidiabetic agents, oral contraceptives, therapeutic drugs for travel sickness, therapeutic drugs for prostatic hypertrophy, therapeutic drugs for pancreatitis, hypnotic inducers, hypnotic-sedative agents, antirheumatoid agents, antiepileptics, cerebral metabolism improving agents, anti-platelet drugs, vitamins, and so on.

More specifically, there are antacids such as calcium carbonate, sodium hydrogencarbonate, magnesium oxide, etc.; antiinflammatory agents such as diclofenac sodium, ketoprofen, indomethacin, flurbiprofen, etc.; analgesic-antipyretic agents such as ibuprofen, acetaminophen, caffeine anhydride, aspirin,

ethenzamide, tolfenamic acid, mefenamic acid, phenacetin, flufenamic acid, salicylamide, aminopyrine, pentazocine, etc.; antiphlogistic agents such as serrapeptidase, lysozyme chloride, etc.; cardiotonics  
5 such as dl-chlorpheniramine maleate, bupranolol hydrochloride, nitroglycerine, isosorbide nitrate, pindolol, propranolol hydrochloride, nifedipine, diltiazem hydrochloride, nisoldipine, benidipine hydrochloride, acebutolol hydrochloride, labetalol hydrochloride,  
10 amlodipine besilate, verapamil hydrochloride, etc.; inorganics preparations such as potassium gluconate, calcium gluconate, sodium chloride, potassium chloride, calcium chloride, etc.; therapeutic agents for digestive ulcer such as glycopyrronium bromide,  
15 proglumide, butylscopolamine bromide, benactyzine methobromide, propantheline bromide, cimetidine, famotidine, omeprazole, lansoprazole, oxethazaine, roxatidine acetate hydrochloride, L-glutamine, L-glutamate-water soluble azulene, sucralfate, etc.;  
20 coronary vasodilators such as phenylpropanolamine hydrochloride, etc.; peripheral and cerebrovasodilators such as beraprost sodium, etc.; antihistamines such as diphenhydramine hydrochloride, etc.; therapeutic drugs for arterial hypertension such as uradipil, etc.;  
25 antitussives-sedative expectrants such as dihydrocodeine phosphate, noscapine, methylephedrine hydrochloride, dextromethorphan hydrobromide, etc.; therapeutic drugs for gout such as bucolome,

colchicine, probenecid, benzbromarone, sulfinpyrazone, allopurinol, etc.; bronchodilators such as aminophylline, theophylline, etc.; antidiabetic agents such as acetohexamide, glibenclamide, tolazamide, 5 tolbutamide, etc.; therapeutic drugs for pancreatitis such as camostat mesylate, etc.

The active ingredient itself may be employed for the present invention, or may be diluted with a diluent that is used generally in the pharmaceutical or 10 food industry. Examples of such diluents include lactose, anhydrous calcium hydrogenphosphate, crystalline cellulose, sucrose, D-mannitol, low substituted hydroxypropyl cellulose, xylitol, erythritol, trehalose, aspartame, etc. Among them, preferred are 15 lactose, anhydrous calcium hydrogenphosphate and crystalline cellulose.

Where the diluent is employed in the powders, the amount of the diluent to be used has no particular limitation and may vary depending on kind of the 20 pharmacologically active ingredient, but the diluent is used generally at least in a 5-fold amount by weight based on the pharmacologically active ingredient.

According to the present invention, the powders for surface modification comprising the 25 pharmacologically active ingredient described above or comprising the pharmacologically active ingredient and optionally further containing the diluent described above are subjected to surface modification with a

surface modifying base material to provide the pharmacologically active ingredient-comprising surface-modified powders having an improved flowability.

Any material can be used as the surface  
5 modifying base material of the present invention so long as the material does not adversely affect the pharmacologically active ingredient and can improve flowability. Preferably, the surface modifying base materials are those capable of physically adhering to  
10 the surface of the powders for surface modification thereby to contribute to improving flowability of the powders. Examples of such surface modifying base materials include light silicic anhydride, talc, stearic acid, magnesium stearate, calcium stearate,  
15 starch, titanium oxide, citric acid, malic acid, adipic acid, hydrous silicon dioxide, calcium carbonate, etc. Preferred are light silicic anhydride, talc, stearic acid, magnesium stearate and calcium stearate, with light silicic anhydride being particularly preferred.  
20 Also, the surface modifying base material has preferably a mean particle size of 10  $\mu\text{m}$  or less; if desired, the surface modifying base material may be ground to powders, which may be provided for use as the base material.

25 For subjecting the surface-modifying powders comprising the aforesaid pharmacologically active ingredient or the active ingredient and the diluent to the surface modification with the surface modifying

base material to improve the flowability, the surface-modifying powders are thoroughly blended with the surface modifying base material. More specifically, the blending can be carried out by any of blending  
5 devices conventionally used for manufacturing pharmaceutical preparations such as devices for surface modification, high speed mixers, high speed agitation granulators, versatile mixer and so on. Examples of such devices include Mechanomill (manufactured by Okada  
10 Seiko Co., Ltd.) Vertical Granulator (manufactured by Powrex), High Speed Mixer (manufactured by Fukae Powtec), Hybridizer, Laboratory Matrix (manufactured by Nara Machinery Co., Ltd.), Theta Composer (manufactured by Tokuju Corporation), etc.

15 The amount of the surface modifying base material described above may vary depending upon kind of the pharmacologically active ingredient used but generally, the surface modifying base material is incorporated in the obtained active ingredient-  
20 comprising surface-modified powders in the amount of approximately 0.1 to 5 wt%, preferably about 1 to about 3 wt%.

In case that the pharmacologically active ingredient having a low melting point or of a sticky  
25 property, such as ibuprofen, is used in the present invention, it is preferred to add finely divided titanium oxide or talc powders to the active ingredient before or after the surface modification described

above at the following production steps, in order to improve tableting problems, i.e., sticking or binding in preparing, e.g., flat tablets. Also where a bitter or stinging active ingredient such as ibuprofen is employed in the present invention, finely divided sweeteners such as erythritol or trehalose are advantageously added to the active ingredient, before or after the surface modification, in the same way as described above.

10                    Preferably, the addition of these components is effected by a so-called multiple layer surface modification method, which involves adding these components to the powders comprising the pharmacologically active ingredient or the pharmacologically active ingredient and the diluent before surface modification or to the pharmacologically active ingredient-comprising surface-modified powders after surface modification, and then dry coating the blend with a high speed mixer, a high speed agitation granulator, a general-purpose kneader, etc. as described above.

25                    Preferably, the components of finely divided titanium oxide, talc, erythritol, trehalose, etc. described above have a mean particle size of 3  $\mu\text{m}$  or less, and the amount of the finely divided components is in the range of 3 wt% or less, based on the total weight of the pharmacologically active surface-modified powders finally obtained.

The thus obtained pharmacologically active ingredient-comprising surface-modified powders generally have a particle size of approximately 20 to 200  $\mu\text{m}$ , preferably about 40 to about 110  $\mu\text{m}$ .

5           Where a pharmacologically active ingredient requiring only a small dose is used to produce the pharmacologically active ingredient-comprising surface-modified powders of the present invention, the following procedures are advantageously employed.

10           For example, when the pharmacologically active ingredient-comprising surface-modified powders are designed to contain 0.02 to 10 wt% of the active ingredient, a diluent such as lactose is added in the course of surface modification to produce the pharmacologically active ingredient-comprising surface-  
15           modified powders. Where lactose is used, large particles of lactose for direct tableting may be used. Suitable examples of the pharmacologically active ingredient used to produce such pharmacologically  
20           active ingredient-comprising surface-modified powders are glycopyrronium bromide, bupranolol hydrochloride and beraprost sodium.

          Unless the effects contemplated in the invention are interfered with, the surface-modified  
25           powders may further contain a variety of additives, which are commonly used in the manufacture of pharmaceutical preparations. Specific examples of such additives will be described hereinafter.



The pharmacologically active ingredient-comprising surface-modified powders of the present invention described above in detail have an excellent flowability. The surface-modified powders of the present invention exhibit flowability at an angle of repose of 42° or less, and more preferably, at an angle of repose of 40° or less. Therefore, the pharmacologically active ingredient-comprising surface-modified powders enable to produce tablets by dry procedures using direct tableting. Thus, the powders can be used not only as substrates for producing the fast disintegrating tablets of the present invention described in the following section, but also as substrates for preparing tablets by dry procedures using other conventional direct tableting. These tablets may also be produced by, for example, admixing the pharmacologically active ingredient-comprising surface-modified powders of the present invention with conventional additives, and tableting the mixture with a direct tableting machine.

According to the present invention, by admixing the pharmacologically active ingredient-comprising surface-modified powders and a disintegrant and directly tableting the mixture, the fast disintegrating tablets of the present invention can be produced. The fast disintegrating tablet of the invention have an appropriate disintegratability and solubility, are disintegrated into a suitable size when

holding water in the oral cavity to cause no stick or choking to the throat and thus make oral medication easy to aged or pediatric patients.

The pharmacologically active ingredient-  
5 comprising surface-modified powders may be used as admixture of a plurality of pharmacologically active ingredient-comprising surface-modified powders using different active components.

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10 Specific examples of the disintegrants used in the present invention include partially alphanized starch, crospovidone (Polyplasdone), crystalline cellulose-carmellose sodium, low substituted hydroxypropyl cellulose, corn starch, potato and other starches, carmellose, carmellose calcium, carmellose  
15 sodium, croscarmellose sodium, carboxymethylstarch sodium, etc. Among them, partially alphanized starch and crospovidone are particularly preferred.

The amount of the disintegrant which is mixed with the pharmacologically active ingredient-comprising  
20 surface-modified powders may vary depending on kind of the active ingredient used, but the disintegrant is used in an amount of generally 10 to 60 wt%, preferably about 20 to 40 wt%, based on the weight of the tablet finally obtained.

25 When a smaller dose of the active ingredient is required as in therapeutic agents for angina pectoris, therapeutic drugs for digestive ulcer, peripheral vasodilators, etc. or a moderate dose is

required as for antiinflammatory-analgesic-antipyretic agents, the disintegrant is added in the amount of generally 10 to 60 wt%, and preferably about 20 to about 40%, based on the total weight of the tablet  
5 finally obtained.

When inorganics or the like requiring a large dose are used as the pharmacologically active ingredient, the disintegrant is added in the amount of generally 10 to 40 wt%, and preferably about 20 to  
10 about 30%, based on the total weight of the tablet finally obtained.

In addition to the disintegrant described above, the surface-modified powders may further contain a variety of additives conventionally employed in the  
15 manufacture of tablets, unless the effects of the invention are interfered with these additives.

Such additives include, for example, binders, acids, foaming agents, artificial sweeteners, flavorings, lubricants, colorants and so on.

20 Examples of the binders include hydroxypropylcellulose, hydroxypropylmethylcellulose 2910, hydroxypropyl starch, gelatin, pullulan and the like. Examples of the acids include citric acid, tartaric acid, malic acid, adipic acid and so on. Examples of  
25 the foaming agents include citric acid, sodium bicarbonate and so on. Examples of the artificial sweeteners include saccharin sodium, glycyrrhizic acid dipotassium salt, aspartame, stevia, thaumatin,

xylitol, erythritol, glucose, and so on. Examples of the flavorings include lemon, orange, grape fruit, grape, menthol, spearmint, peppermint, vanilla, cinnamon, and the like. Examples of the lubricants  
5 include magnesium stearate, talc, sucrose fatty acid esters, polyethyleneglycol, stearic acid and the like. Examples of the colorants include various food colorants, e.g. FD & C Yellow No. 5, FD & C RED No.2, FD & C Blue No.2, etc., food lakes, red iron oxide and  
10 so on.

One or more of these additives can be timely added in appropriate proportions, for example, at any step in the course of blending or before and after blending the pharmacologically active ingredient-  
15 comprising surface-modified powders with the disintegrant.

In the present invention, it is advantageous to use, among others, crystalline cellulose (trade name: CEOLUS, manufactured by Asahikasei Corporation)  
20 as the additive, in combination with the disintegrant, since the hardness of the tablets obtained is increased. Where crystalline cellulose is added to the powders, the hardness of the resulting tablet is enhanced, while the tablet retains its rapid disinte-  
25 grating property. The crystalline cellulose is added to the powders to have a proportion of 10 to 70 wt%, based on the total weight of the tablet finally obtained.

The blending of the pharmacologically active ingredient-comprising surface-modified powders with the disintegrant and optionally additives can be carried out by any blending techniques such as mixing, kneading, sieving and so on, which are conventionally used in the course of manufacturing pharmaceutical preparations. Specifically, a V-Shaped Mixer, Gyro Shifter, Theta Composer (manufactured by Tokuju Corporation), Vertical Granulator (manufactured by Powrex), High Speed Mixer (manufactured by Fukae Powtec), Laboratory Matrix (manufactured by Nara Machinery Co., Ltd.), etc. can be employed.

For tabletting the blend or mixture thus obtained, devices conventionally used for molding of tablets can be employed. For example, a single tabletting machine, a rotary tabletting machine, a full-automated rotary tabletting machine (manufactured by Hata Iron Works), etc. are available.

In tabletting with the above tabletting machines, a compression pressure greatly changes depending on tablet size. When using a pestle of 8 mm in diameter, the compression pressure is generally set under 190 to 1,990 Kg/cm<sup>2</sup>, with a pestle of 10 mm in diameter, generally under 250 to 1,920 Kg/cm<sup>2</sup>, and with a pestle of 20 mm in diameter, generally under 520 to 1,320 Kg/cm<sup>2</sup>. The tablet is compression-molded to have an appropriate strength well resistant to the steps of storage, packaging and transportation.

As described above, the fast disintegrating tablets of the present invention can be extremely readily produced by dry procedures using production devices conventionally available, without requiring any  
5 complex step. Moreover, the thus produced fast disintegrating tablets are excellent in solubility and disintegratability.

The fast disintegrating tablets of the present invention have a suitable disintegratability  
10 and solubility to be disintegrated to a desired size when holding water in the oral cavity so that the tablets are neither adhered to nor choked in the throat, and are easy for administration to aged or pediatric patients. Accordingly, the tablets of the  
15 present invention can be advantageously used for the treatment and prevention of diseases in patients, particularly aged or pediatric patients.

Furthermore, the fast disintegrating tablets of the present invention are excellent in storage and  
20 stability over a long period of time, because the tablets possess a desired strength. The tablets of the present invention retain a mechanical strength sufficient to resist destruction when the tablets are taken by the patient, for example, when they are taken out of  
25 PTP packages. Therefore, the fast disintegrating tablets of the invention can be advantageously used for the patient who should be medicated depending on the active ingredient contained, for the treatment and

prevention of diseases in patients, particularly aged or pediatric patients.

Hereinafter, the present invention will be described in more detail, with reference to EXAMPLES  
5 but is not deemed to be limited thereto.

#### EXAMPLE 1

A high speed agitation granulator (Laboratory Matrix LMA10, manufactured by Nara Machinery Co., Ltd.) was charged with 2 parts by weight of light silicic  
10 anhydride based on 100 parts by weight of ibuprofen to examine the conditions for surface modification. A mean particle size became constant when the time for surface modification showed 15 minutes. Measurement of the angle of repose 25 minutes after revealed that  
15 flowability was markedly improved. It was thus confirmed that the powders containing the original drug for direct tableting, namely, the pharmacologically active ingredient-comprising surface-modified powders of the present invention were obtained. The procedures  
20 and results are shown in TABLE 1.

TABLE 1

<u>Time for Surface</u> <u>Modification (min.)</u>	<u>Mean Particle</u> <u>Size (<math>\mu\text{m}</math>)<sup>*1</sup></u>	<u>Angle of</u> <u>Repose (<math>^{\circ}</math>)<sup>*2</sup></u>
0	50.5	53
3	46.1	-
5	48.0	45
10	55.8	42
15	57.7	40
20	57.2	39
25	57.3	39

Conditions for surface modification:

main impeller: 300 rpm

granulation impeller: 1,500 rpm

\*1: The mean particle size was measured using  
5 a Laser diffraction size analyzer LDSA-1400A (manufactured by Tohnichi Computer Application Co., Ltd.).

\*2: The angle of repose was measured with a powder tester (manufactured by Hosokawa Micron Co., Ltd.).

## 10 EXAMPLE 2

A high speed agitation granulator (Laboratory Matrix LMA10, manufactured by Nara Machinery Co., Ltd.) was charged with 1 part by weight of light silicic anhydride based on 100 parts by weight of potassium  
15 gluconate to examine the conditions for surface modification in the same manner as in EXAMPLE 1. The



results are shown in TABLE 2.

TABLE 2

<u>Time for Surface</u> <u>Modification (min.)</u>	<u>Mean Particle</u> <u>Size (<math>\mu</math>m)</u>	<u>Angle of</u> <u>Repose (<math>^{\circ}</math>)</u>
0	111.3	41
5	123.6	39
10	122.5	37
15	121.5	37

Conditions for surface modification:

main impeller: 300 rpm

granulation impeller: 1,500 rpm

- 5 Measurement of the mean particle size and angle of repose:

The same devices as in EXAMPLE 1 were used.

- The results of EXAMPLES 1 and 2 reveal that by adding light silicic anhydride to the pharmaco-
- 10 logically active ingredient to effect the surface modification, the flowability (angle of repose) of the pharmacologically active ingredient-comprising surface-modified powders of the present invention was markedly improved to give the flowability sufficient to perform
- 15 direct tableting continuously. The results further reveal that the time required for surface modification was at least 5 minutes, preferably 10 to 20 minutes.

Furthermore, the time required for surface modification can be judged by the time when the angle of repose becomes 40° or less.

The results of EXAMPLES 1 and 2 reveal that  
5 when the active ingredient has a particle size of 20  $\mu\text{m}$  or more, the surface-modified product with a good quality, i.e., the pharmacologically active ingredient-comprising surface-modified powders of the invention can be obtained, since the mean particle size of  
10 ibuprofen and potassium gluconate were found to be 50.5  $\mu\text{m}$  (10% particle size: 19.2  $\mu\text{m}$ , 90% particle size: 101.6  $\mu\text{m}$ ) and 111.3  $\mu\text{m}$ , respectively. The pharmacologically active ingredient of at least 50  $\mu\text{m}$  is preferred for use in the present invention.

15 EXAMPLE 3

A high speed agitation granulator (Laboratory Matrix LMA10, manufactured by Nara Machinery Co., Ltd.) was charged with ibuprofen and light silicic anhydride in the respective amounts shown in TABLE 3 below.

20 Surface modification was performed for 25 minutes (conditions for the surface modification: a main impeller of 300 rpm, a granulation impeller of 1,500 rpm). Next, the whole amount of the pharmacologically active ingredient-comprising surface-modified powders  
25 of the present invention obtained above were taken out of the granulator. The remaining components given in TABLE 3 below, i.e., citric acid, partially alphanized

starch (manufactured by Asahikasei Corporation, trade name: PCS), crystalline cellulose (manufactured by Asahikasei Corporation, Avicel PH301) and magnesium stearate were added to the powders, followed by mixing with a V-10 blender (manufactured by Tokuju Corporation) for 5 minutes. The mixture was tableted with a pestle of 10 mm in diameter and 7.5 mmR using a fully automated rotary tabletting machine (manufactured by Hata Iron Works). Thus, the fast disintegrating tablets of the present invention were produced. Flavorings, sweeteners and so on may be incorporated to improve the taste.

TABLE 3

## Formulation

<u>Component</u>	<u>Amount Added (unit: g)</u>
Ibuprofen	800
Light silicic anhydride	16
Citric acid	200
Partially alphanized starch	956
Crystalline cellulose	380
Magnesium stearate	48
Total	2400

## EXAMPLE 4

The same formulation as in EXAMPLE 3 was surface-modified under the same conditions as those of EXAMPLE 3 and the experiment was carried out in the same way, except that the disintegrant was changed to

crospovidone (the amount was the same). A high speed agitation granulator (Laboratory Matrix LMA10, manufactured by Nara Machinery Co., Ltd.) was charged with ibuprofen and light silicic anhydride in the  
5 respective amounts indicated in TABLE 4 below. Surface modification was performed for 25 minutes (conditions for the surface modification: main impeller of 300 rpm, granulation impeller of 1,500 rpm). Next, the whole amount of the pharmacologically active ingredient-  
10 comprising surface-modified powders of the present invention obtained above were taken out of the granulator. The remaining components given in TABLE 4 below, i.e., citric acid, crospovidone (manufactured by ISP Japan, trade name: Polyplasdone XL), crystalline  
15 cellulose and magnesium stearate were added to the powders, followed by mixing with a V-10 blender (manufactured by Tokuju Corporation) for 5 minutes. The mixture was tableted with a pestle of 10 mm in diameter and 7.5 mmR using a fully automated rotary  
20 tabletting machine (manufactured by Hata Iron Works). Thus, the fast disintegrating tablets of the present invention were produced. Flavorings, sweeteners and so on may be incorporated to improve taste.

TABLE 4

Formulation	
<u>Component</u>	<u>Amount Added (unit: g)</u>
Ibuprofen	800
Light silicic anhydride	16
Citric acid	200
Crospovidone	956
Crystalline cellulose	380
Magnesium stearate	48
Total	2400

## EXAMPLE 5

Sub B2  
A high speed agitation granulator (Laboratory Matrix LMA10, manufactured by Nara Machinery Co., Ltd.) was charged with potassium gluconate and light silicic anhydride in the respective amounts indicated in TABLE 6 below. Surface modification was performed for 15 minutes (conditions for the surface modification: main impeller of 300 rpm, granulation impeller of 1,500 rpm). Next, the whole amount of the pharmacologically active ingredient-comprising surface-modified powders of the present invention obtained above were taken out of the granulator. The remaining components given in TABLE 5 below, i.e., partially alphanized starch, glucono delta lactone, erythritol, crystalline cellulose and magnesium stearate were added to the powders, followed by mixing with a V-10 blender (manufactured by Tokuju Corporation) for 5 minutes. The mixture was then tableted with a pestle for odd-

B3  
shaped tablets (16 mm × 7 mm) using a fully automated rotary tabletting machine (manufactured by Hata Iron Works). Thus, the fast disintegrating tablets of the present invention were produced. Flavorings, 5 sweeteners and so on may be incorporated to improve taste.

TABLE 5

sub B4

Formulation	
<u>Component</u>	<u>Amount Added (unit: g)</u>
Potassium gluconate	500
Light silicic anhydride	5
Partially alphanized starch	215
Glucono delta lactone	12
Erythritol	50
Crystalline cellulose	100
Magnesium stearate	18
Total	900

## EXAMPLE 6

A high speed agitation granulator (Laboratory Matrix LMA10, manufactured by Nara Machinery Co., Ltd.) was charged with potassium gluconate and light silicic anhydride in the respective amounts indicated in TABLE 6 below. Surface modification was performed for 15 minutes (conditions for the surface modification: main impeller of 300 rpm, granulation impeller of 1,500 rpm). Next, the whole amount of the pharmacologically active ingredient-comprising surface-modified powders of the present invention obtained above were taken out

of the granulator. The remaining components given in  
 TABLE 6 below, i.e., crospovidone, glucono delta  
 lactone, crystalline cellulose and magnesium stearate  
 were added to the powders, followed by mixing with a V-  
 5 10 blender (manufactured by Tokujin Corporation) for 5  
 minutes. The mixture was then tableted with a pestle  
 for odd-shaped tablets (19 mm X 8 mm) using a fully  
 automated rotary tabletting machine (manufactured by  
 Hata Iron Works). Thus, the fast disintegrating  
 10 tablets of the present invention were produced.  
 Flavorings, sweeteners and so on may be incorporated to  
 improve taste.

TABLE 6

## Formulation

<u>Component</u>	<u>Amount Added (unit: g)</u>
Potassium gluconate	1000
Light silicic anhydride	10
Crospovidone	238
Glucono delta lactone	24
Crystalline cellulose	100
Magnesium stearate	28
Total	1400

## EXAMPLE 7

A high speed agitation granulator (Vertical  
 15 Granulator FM-VG-01, manufactured by Powrex) was  
 charged with bupranolol hydrochloride and lactose G.  
 After blending with a main impeller and a granulation

impeller, both at 500 rpm for 1 minute, 2 wt% of light silicic anhydride was added and surface modification was conducted for 10 minutes under the same conditions. The remaining components given in TABLE 7 below, i.e., partially alphanized starch and magnesium stearate were added to the powders, followed by blending a Transparent Micro V-Mixer (manufactured by Tsutsui Scientific Instruments Co., Ltd.) for 15 minutes. The mixture was then tableted with a flat-faced beveled edged pestle of 8.5 mm in diameter using a fully automated rotary tabletting machine (manufactured by Hata Iron Works). Thus, the fast disintegrating tablets of the present invention were produced. Flavorings, sweeteners and so on may be incorporated to improve taste.

TABLE 7

Formulation		
	<u>Component</u>	<u>Amount Added (unit: g)</u>
	Bupranolol hydrochloride	10
	Lactose G	107.6
	Light silicic anhydride	2.4
	Partially alphanized starch	89.2
	Magnesium stearate	0.8
	Total	210

## EXAMPLE 8

A high speed agitation granulator (Vertical Granulator FM-VG-01, manufactured by Powrex) was



charged with glycopyrronium bromide and lactose  
(manufactured by Freund Industrial Co., Ltd., trade  
name: DAI-LACTOSE S). After blending with a main  
impeller and a granulation impeller, both at 500 rpm,  
5 for 1 minute, 1 wt% of light silicic anhydride was  
added and surface modification was conducted for 15  
minutes under the same conditions. The remaining  
components shown in TABLE 8 below, i.e., crystalline  
cellulose, partially alphanized starch, erythritol and  
10 magnesium stearate were added to the powders, followed  
by blending a Transparent Micro V-Mixer (manufactured  
by Tsutsui Scientific Instruments Co., Ltd.) for 15  
minutes. The mixture was then tableted with a pestle  
of 8.5 mm in diameter and 6.5R using a fully automated  
15 rotary tableting machine (manufactured by Hata Iron  
Works). Thus, the fast disintegrating tablets of the  
present invention were produced. Flavorings,  
sweeteners and so on may be incorporated to improve  
taste.

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TABLE 8

Formulation		
	<u>Component</u>	<u>Amount Added (unit: g)</u>
	Glycopyrronium bromide	1
	Lactose	99
	Light silicic anhydride	1
	Crystalline cellulose	30
	Partially alphanized starch	100
	Erythritol	16.5
	Magnesium stearate	2.5
	Total	250

## EXAMPLE 9

1) A high speed agitation granulator  
(Vertical Granulator FM-VG-01, manufactured by Powrex)  
was charged with ibuprofen and 2 wt% of light silicic  
5 anhydride based on ibuprofen. Surface modification was  
conducted for 25 minutes under the following condi-  
tions: a main impeller at 500 rpm and a granulation  
impeller at 500 rpm.

2) Next, a high speed agitation granulator  
10 (Vertical Granulator FM-VG-01, manufactured by Powrex)  
was charged with acetaminophen and 2 wt% of light  
silicic anhydride based on acetaminophen. Surface  
modification was conducted for 25 minutes under the  
following conditions: a main impeller at 500 rpm and a  
15 granulation impeller at 500 rpm.

3) Next, a high speed agitation granulator  
(Vertical Granulator FM-VG-01, manufactured by Powrex)

[illegible]

4) The remaining components shown in TABLE 9 below, i.e., citric acid, partially alphanized starch, lactose, crystalline cellulose and magnesium stearate were added to the respective three pharmacologically active ingredient-comprising surface-modified powders, followed by blending a V-10 blender (manufactured by Tokuju Corporation) for 5 minutes. Each mixture was then tableted with a pestle of 10 mm in diameter and 7.5 mmR using a fully automated rotary tableting machine (manufactured by Hata Iron Works). Thus, the fast disintegrating tablets of the present invention were produced. Flavorings, sweeteners and so on may be incorporated to improve taste.

TABLE 9

## Formulation

<u>Component</u>	<u>Amount Added (unit: g)</u>
Ibuprofen	75
Acetaminophen	150
Anhydrous caffeine	60
Light silicic anhydride	5.7
Citric acid	20
Partially alphanized starch	232.3
Lactose	100
Crystalline cellulose	50
Magnesium stearate	7
Total	700

## TEST EXAMPLE 1

In order to explain the effects achieved by the present invention in more detail, tablet characteristics were determined with the fast disintegrating tablets of the invention obtained in EXAMPLES and commercial products, and comparison was made between the tablets of the invention and the commercial products. The results are shown in TABLES 10 and 11. It is understood by comparing TABLES 10 and 11 that the fast disintegrating tablets obtained in the present invention are excellent in disintegratability and yet maintain a suitable strength. It is also confirmed that partially alphanized starch and crospovidone were most suitable as the disintegrant.

Characteristic data of the experimental tablets  
prepared in EXAMPLES:

TABLE 10

No. Example	1-1 3	1-2 4	2-1 5	2-2 6	3 7	4 8	5 9
Weight (mg)	300	300	900	1400	210	250	350
Thickness of tablet (mm)	5.4	5.2	6.2	9.2	5.1	6.0	5.8
Diameter of tablet (mm)	10.1	10.1	16×7	19×8	8.6	8.6	10.1
Hardness (kg)	4.0	6.0	4.8	6.1	3.1	2.7	5.3
Disintegration time (1)	29 secs.	15 secs.	120 secs.	29 secs.	45 secs.	30 secs.	34 secs.
Disintegration time (2)	62 secs.	37 secs.	186 secs.	120 secs.	79 secs.	30 secs.	58 secs.

#### Hardness:

The hardness is expressed as a mean value of  
5 five measurements as measured with Kiya type Hardness  
Tester.

(Hardness tester: HARDNESS TESTER (manufac-  
tured by KIYA))

#### Disintegration time (1):

10 The disintegration time was measured with a  
disintegration tester specified in The Pharmacopoeia of  
Japan, 13th edition (no disk). The results indicate a  
mean value of six runs.

(Disintegration tester: table disintegration  
15 tester T-4H (manufactured by Toyama Sangyo Co., Ltd.))

Disintegration time (2):

A sieve of 5.5 mesh was put in a beaker charged with 300 mL of water. One tablet was placed in the beaker. The total elapsed time required for the  
5 tablet to disintegrate, completely pass through the sieve and fall out of the mesh was recorded (distilled water: 23°C). The disintegration time is the average of the time recorded for 2 runs.

Characteristic data of the commercial products:

TABLE 11

No. of Commercial Tablet	Tablet 1	Tablet 2	Tablet 3	Tablet 4
Preparation form	Dragee	Film-coated	Film-coated	Uncoated
Weight (mg)	224	1245	178	203
Thickness of tablet (mm)	4.8	7.6	4.5	2.7
Diameter of tablet (mm)	8.1	19×8	7.7	8.6
Hardness (kg)	6.9	≥20	9.1	4.5
Disintegration time (1)	10 mins.	≥30 mins.	3 mins.	1 min.
Disintegration time (2)	≥30 mins.	≥30 mins.	7 mins.	80 secs.

#### 10 Hardness:

The hardness is expressed as a mean value of five measurements as measured with Kiya type Hardness Tester.

(Hardness tester: HARDNESS TESTER (manufactured by KIYA))  
15

Disintegration time (1):

The disintegration time was measured with a disintegration tester specified in The Pharmacopoeia of Japan, 13th edition (no disk). The results indicate a mean value of six runs.

(Disintegration tester: table disintegration tester T-4H (manufactured by Toyama Sangyo Co., Ltd.))

Disintegration time (2):

A sieve of 5.5 mesh was put in a beaker charged with 300 mL of water. One tablet was placed in the beaker. The total elapsed time required for the tablet to disintegrate, completely pass through the sieve and fall out of the mesh was recorded (distilled water: 23°C). The disintegration time is the average of the time recorded for 2 runs.

#### EXAMPLE 10

The blended powders produced in EXAMPLE 3 were tableted with a pestle having flat-faced beveled edges of 10 mm in diameter. Tableting problem (sticking to the pestle) was observed.

The material stuck to the pestle was found to be ibuprofen. It was considered to be caused by difference in shape of the pestle.

In order to solve the tableting problem, titanium oxide (manufactured by Toho Titanium K.K., trade name: Highly Pure Titanium Oxide) was coated onto

the surface of the surface-modified powders to form multiple layers. Thus, the fast disintegrating tablets could be produced.

The procedures for producing the fast  
5 disintegrating tablets are described below.

A high speed agitation granulator (Laboratory Matrix LMA10, manufactured by Nara Machinery Co., Ltd.) was charged with ibuprofen and light silicic anhydride in the respective amounts shown in TABLE 12 below.

10 Surface modification was performed for 25 minutes (conditions for the surface modification: a main impeller of 300 rpm, a granulation impeller of 1,500 rpm). Next, titanium oxide having a mean particle size of 2.1  $\mu\text{m}$  was added as indicated in TABLE 12 below to  
15 perform dry coating for 5 minutes under the same conditions. Thus, the multilayered surface-modified powders with titanium oxide coating on the surface of the powders were prepared.

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B10  
20 Thereafter, the whole amount of the pharmacologically active ingredient-comprising surface-modified powders of the present invention obtained above were taken out of the granulator. The remaining components given in TABLE 12 below, i.e., citric acid (manufactured by Wako Pure Chemical Industries Ltd.),  
25 partially alphanized starch (manufactured by Asahikasei Corporation), crystalline cellulose (manufactured by Asahikasei Corporation, CEOLUS), talc (manufactured by Shokozan Mining Co., Ltd.) and magnesium stearate



(manufactured by Kyodo Yakuhin K.K.) were added to the powders, followed by mixing with a V-10 blender (manufactured by Tokuju Corporation) for 5 minutes. By tabletting the mixture with a pestle of 10 mm in diameter having flat-faced beveled edges using a tabletting machine, the tabletting problem was eliminated. Thus, the fast disintegrating tablets of the present invention were produced. The results indicate that by the multilayered surface modifying procedures, there could be obtained the fast disintegrating tablets available for low melting or strongly sticky drugs, irrespective of the shape of a pestle.

TABLE 12

Formulation		
<u>Component</u>	<u>Amount Added (unit: g)</u>	
Ibuprofen	800	
Light silicic anhydride	8	
Titanium oxide	24	
Citric acid	136	
Partially alphanized starch	956	
Crystalline cellulose	380	
Magnesium stearate	48	
Talc	48	
Total	2400	

## EXAMPLE 11

Taste comparison was performed with the tablets prepared in EXAMPLE 10. A strongly stinging

taste spread over the entire tongue. The irritating component was found to be ibuprofen.

Therefore, an attempt to mask the stinging taste of the ibuprofen-containing fast disintegrating tablets and change them to compatible medicaments easy to be taken was made to alleviate the irritation of a drug particle carrier by multilayered surface modifying technique using the surface modification in combination with dry coating as in EXAMPLE 10. Finely divided erythritol (mean particle size: 1.3  $\mu\text{m}$ ) was used to reduce the stinging taste of ibuprofen. Erythritol was again added to the powders at the final stage to improve the taste.

The procedures of making pharmaceutical preparations with an improved taste and further functioning as a fast disintegrating tablet are described below.

A high speed agitation granulator (Laboratory Matrix LMA10, manufactured by Nara Machinery Co., Ltd.) was charged with ibuprofen and light silicic anhydride in the respective amounts shown in TABLE 13 below. Surface modification was performed for 25 minutes (conditions for the surface modification: a main impeller of 300 rpm, a granulation impeller of 1,500 rpm). Next, titanium oxide having a mean particle size of 2.1  $\mu\text{m}$  and as a sweetener, erythritol finely divided with a jet mill in a mean particle size of 1.3  $\mu\text{m}$  were added as indicated in TABLE 13 below to perform dry

coating for 5 minutes under the same conditions. Thus, the multilayered surface-modified powders, on the surface of which titanium oxide and jet mill-grounded erythritol had been coated were prepared.

5 Then, the whole amount of the pharmacologically active ingredient-comprising surface-modified powders of the present invention obtained above were taken out of the granulator. The remaining components given in TABLE 13 below, namely, citric acid  
10 (manufactured by Wako Pure Chemical Industries Ltd.), partially alphanized starch (manufactured by Asahikasei Corporation), crystalline cellulose (manufactured by Asahikasei Corporation, CEOLUS), talc (manufactured by Shokozan Mining Co., Ltd.), erythritol (manufactured by  
15 Nikken Chemical Industry Co., Ltd.), a flavoring agent (manufactured by Ogawa Perfumery Co., Ltd.) and magnesium stearate (manufactured by Kyodo Yakuhin K.K.) were added to the powders, followed by blending with a V-10 blender (manufactured by Tokuju Corporation) for 5  
20 minutes. Any tableting problem that might be caused by tableting the blend with a pestle of 10 mm in diameter having flat-faced beveled edges using a tableting machine was not noted. Moreover, the thus produced fast disintegrating tablets of the present  
25 invention were improved on the stinging taste. The results indicate that by the multilayered surface modifying technique, the fast disintegrating tablets were found to be available for improving the taste of

drugs having a bitter or stinging taste.

TABLE 13

Formulation	
<u>Component</u>	<u>Amount Added (unit: g)</u>
Ibuprofen	400
Light silicic anhydride	4
Titanium oxide	4
Finely divided erythritol	12
Citric acid	40
Erythritol	400
Partially alphanized starch	480
Crystalline cellulose	1000
Flavoring agent (orange)	12
Magnesium stearate	24
Talc	24
Total	2400

## EXAMPLE 12

It was examined if the order of the multi-layered surface modification technique used in EXAMPLE 12, namely, the surface modification and dry coating, would affect the tablet characteristics. For the comparison purpose, the same formulation as that of EXAMPLE 11 was used in this EXAMPLE.

The procedures are described below.

A high speed agitation granulator (Laboratory Matrix LMA10, manufactured by Nara Machinery Co., Ltd.) was charged with ibuprofen, titanium oxide having a mean particle diameter of 2.1  $\mu\text{m}$  and finely divided erythritol (a mean particle size: 1.3  $\mu\text{m}$ ) in the

respective amounts shown in TABLE 14 below. Dry coating was performed for 5 minutes (a main impeller of 300 rpm, a granulation impeller of 1,500 rpm).

Subsequently, light silicic anhydride was added to the blend as indicated in TABLE 14 below. Surface modification was performed for 25 minutes under the same conditions to produce the multilayered surface-modified powders containing the anti-adhesion agent and the sweetener.

10               Next, the whole amount of the pharmacologi-  
cally active ingredient-comprising surface-modified  
powders of the present invention obtained above were  
taken out of the granulator. The remaining components  
given in TABLE 14 below, namely, citric acid (manufac-  
15               tured by Wako Pure Chemical Industries Ltd.), partially  
alphanized starch (manufactured by Asahikasei Corpora-  
tion), crystalline cellulose (manufactured by  
Asahikasei Corporation, CELULUS), talc (manufactured by  
Shokozan Mining Co., Ltd.), erythritol (manufactured by  
20               Nikken Chemical Industry Co., Ltd.), a flavoring agent  
(manufactured by Ogawa Perfumery Co., Ltd.) and  
magnesium stearate (manufactured by Kyodo Yakuhin K.K.)  
were added to the powders, followed by blending with a  
V-10 blender (manufactured by Tokuju Corporation) for 5  
25               minutes. The blend was tableted with a pestle of 10 mm  
in diameter having flat-faced beveled edges using a  
tableting machine but no tableting problem was noted.  
Moreover, the thus produced fast disintegrating tablets

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of the present invention had a quality equivalent to those obtained in EXAMPLE 11 in terms of improvement in the stinging taste. The results indicate that by the multilayered surface modifying technique, the fast disintegrating tablets were found to be available not only for low melting or strongly sticky drugs but also for improving the taste of drugs having a bitter or stinging taste. It was confirmed that even if the order of adding the surface modifiers is changed, the tablet preparations can be obtained with an equivalent quality.

TABLE 14

Formulation	
<u>Component</u>	<u>Amount Added (unit: g)</u>
Ibuprofen	400
Titanium oxide	4
Finely divided erythritol	12
Light silicic anhydride	4
Citric acid	40
Erythritol	400
Partially alphanized starch	480
Crystalline cellulose	1000
Flavoring agent (orange)	12
Magnesium stearate	24
Talc	24
Total	2400

## EXAMPLE 13

Using trehalose instead of the sweetener

erythritol used in EXAMPLES 11 and 2, it was examined if kind of the sweetener would affect the tablet characteristics. The multilayered surface modifying technique, namely, the order and formulation of the surface modification and the dry coating were the same as in EXAMPLE 12.

The procedures are described below.

A high speed agitation granulator (Laboratory Matrix LMA10, manufactured by Nara Machinery Co., Ltd.) was charged with ibuprofen, titanium oxide having a mean particle diameter of 2.1  $\mu\text{m}$  and finely divided trehalose (a mean particle size: 1.4  $\mu\text{m}$ ) (manufactured by Asahikasei Corporation) in the respective amounts shown in TABLE 15 below. Dry coating was performed for 5 minutes (a main impeller of 300 rpm, a granulation impeller of 1,500 rpm).

Subsequently, light silicic anhydride was added to the blend as indicated in TABLE 15 below. Surface modification was performed for 25 minutes under the same conditions to produce the multilayered surface-modified powders containing the anti-adhesion agent and the sweetener.

Next, the whole amount of the pharmacologically active ingredient-comprising surface-modified powders of the present invention obtained above were taken out of the granulator. The remaining components given in TABLE 15 below, namely, citric acid (manufactured by Wako Pure Chemical Industries Ltd.), partially

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alphanized starch (manufactured by Asahikasei Corpora-  
tion), crystalline cellulose (manufactured by  
Asahikasei Corporation, CEOLUS), talc (manufactured by  
Shokozan Mining Co., Ltd.), erythritol (manufactured by  
5 Nikken Chemical Industry Co., Ltd.), a flavoring agent  
(manufactured by Ogawa Perfumery Co., Ltd.) and  
magnesium stearate (manufactured by Kyodo Yakuhin K.K.)  
were added to the powders, followed by blending with a  
V-10 blender (manufactured by Tokuju Corporation) for 5  
10 minutes. The blend was tableted with a pestle of 10 mm  
in diameter having flat-faced beveled edges using a  
tableting machine but no tableting problem was noted.  
The thus produced fast disintegrating tablets had a  
quality comparable to those obtained in EXAMPLE 12,  
15 indicating that trehalose is likewise available for the  
multilayered surface modification technique.

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TABLE 15

Formulation	
<u>Component</u>	<u>Amount Added (unit: g)</u>
Ibuprofen	400
Titanium oxide	4
Finely divided trehalose	12
Light silicic anhydride	4
Citric acid	40
Erythritol	400
Partially alphanized starch	480
Crystalline cellulose	1000
Flavoring agent (orange)	12
Magnesium stearate	24
Talc	24
Total	2400

## TEST EXAMPLE 2

In order to explain the effects achieved by the present invention in more detail, tablet characteristics were determined with the fast disintegrating tablets of the invention obtained in EXAMPLES 10 through 13. The results are shown in TABLE 16. The results reveal that the fast disintegrating tablets obtained in the present invention are excellent in disintegratability and yet maintain a suitable strength. No tableting problem (sticking to the pestle) was noted with the tablets obtained in EXAMPLES 10 to 13 and with the fast disintegrating tablets obtained in EXAMPLES 11 to 13, even the strongly stinging taste of ibuprofen was improved.

TABLE 16

Example	10	11	12	13
Pestle	10 mm $\phi$ , flat-faced beveled edge			
Sticking to pestle	none	none	none	none
Weight (mg)	300	300	300	300
Thickness of tablet (mm)	3.5	3.5	3.5	3.5
Diameter of tablet (mm)	10.2	10.1	10.1	10.2
Hardness (kg)	7.6	8.5	7.1	8.8
Disintegration time (1)	23 secs.	26 secs.	22 secs.	25 secs.
Disintegration time (2)	70 secs.	74 secs.	70 secs.	73 secs.
Taste (stinging)	yes	none <sup>*1</sup>	none	none

#### Hardness:

The hardness is expressed as a mean value of five measurements as measured with Kiya type Hardness Tester.

5 (Hardness tester: HARDNESS TESTER (manufactured by KIYA))

#### Disintegration time (1):

The disintegration time was measured with a disintegration tester specified in The Pharmacopoeia of Japan, 13th edition (no disk). The results indicate a mean value of six runs.

(Disintegration tester: table disintegration tester T-4H (manufactured by Toyama Sangyo Co., Ltd.))

#### Disintegration time (2):

15 A sieve of 5.5 mesh was put in a beaker charged with 300 mL of water. One tablet was placed in

the beaker. The total elapsed time required for the tablet to disintegrate, completely pass through the sieve and fall out of the mesh was recorded (distilled water: 23°C). The disintegration time is the average  
5 of the time recorded for 2 runs.

\*1: When taken together with water, there was no stinging taste and the stinging taste was alleviated when taken without water.

#### INDUSTRIAL APPLICABILITY

10           The fast disintegrating tablets of the present invention can be produced by the dry method in an extremely simple way, without requiring any complex procedures, using conventionally available devices/  
15           equipments. Moreover, the thus produced fast disintegrating tablets exhibit excellent dissolution and disintegration properties.

          The fast disintegrating tablets of the present invention have a suitable disintegratability and solubility to be disintegrated to an appropriate  
20           size when holding water in the oral cavity so that the tablets are neither adhered to nor choked in the throat, and are easy for administration to aged or pediatric patients, and thus are advantageously used for the prevention or treatment of diseases in  
25           patients, particularly aged and pediatric patients.

          The fast disintegrating tablets of the present invention have a sufficient strength and thus,

are excellent for storage and stability over a long period of time. The fast disintegrating tablets of the invention yet maintain a strength sufficient to resist destruction upon administration, for example, when they  
5 are taken out of PTP packages. Therefore, the tablets of the invention can be advantageously used for the prevention or treatment of diseases in patients, particularly aged and pediatric patients.

Furthermore, by subjecting the pharmacologi-  
10 cally active ingredients to surface modification using the surface modifying base material including light silicic anhydride, the pharmacologically active ingredient-comprising surface-modified powders having a good flowability can be obtained. The powders enable  
15 to produce the fast disintegrating tablets of the present invention by the dry production method.

Moreover, the multilayered surface modification technique by the dry coating in combination with the aforesaid surface modification using titanium oxide  
20 or erythritol having a mean particle size of 3  $\mu\text{m}$  or less enables to produce tablets free of any tableting problem and also enables to produce tablets with an improved taste.